

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202832Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 202-832
Priority or Standard S

Submit Date(s) January 31, 2011
Received Date(s) February 1, 2011
PDUFA Goal Date January 7, 2012
Division / Office DPARP/ODE II

Reviewer Name(s) Xu Wang, M.D., Ph.D.
Review Completion Date December 7, 2011

Established Name Sodium Chloride Injection, USP
0.9%
(Proposed) Trade Name None
Therapeutic Class Saline
Applicant Medefil, Inc.

Formulation(s) Solution in pre-filled plastic
syringes for single use
Dosing Regimen
Indication(s) Dilution or Dissolution of Drugs
Intended Population(s) Adults and children

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

“Approval” action is recommended for the application from a clinical perspective.

The proposed product is normal saline (0.9% sodium chloride) in pre-filled syringes. This is a 505(b)(2) application. The reference products are 2 products of 0.9% sodium chloride injection manufactured by Hospira and (b) (4) (NDA 18-803 and ANDA 88-912). The proposed indication is for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection.

Of note is that this same product has been evaluated by the Center for Devices and Radiological Health (CDRH) under the 510(k) process and it was determined to be “substantially equivalent to legally marketed predicate devices”, and, thus, could be marketed as a device with the intention for use of flushing compatible intravenous tubing and/or indwelling intravenous access devices.

There are no clinical data in this NDA submission. There are no significant safety concerns with the use of small amounts of sodium chloride 0.9% solution for the purpose of diluting or dissolving marketed drug products. This clinical review is to summarize the development background of the proposed product, and to fulfill the procedural requirement from a regulatory perspective.

1.2 Risk Benefit Assessment

The proposed product is normal saline (0.9% sodium chloride) solution in pre-filled plastic syringes for single use. The drug labeling indication is for diluting or dissolving compatible drugs. There are no clinical data in this NDA submission. As a physiologic solution, there is minimal risk to patients who receive small quantities of 0.9% sodium chloride. Thus, the risk and benefit in clinical usage of the proposed product will be determined by the specific drug to be diluted or dissolved. There are many approved and currently marketed saline products on the market. No new safety concerns are apparent for the use of the proposed normal saline solution in pre-filled plastic syringes for single use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) application for sodium chloride injection, USP, 0.9% in plastic syringes submitted by Medefil, Inc. The Applicant cites 2 products of 0.9% sodium chloride injection manufactured by Hospira and (b) (4) (NDA 19-217 and ANDA 88-912) as the reference products. The originally proposed trade name for the product was (b) (4), however, on July 11, 2011, the Applicant withdrew the proposed name. At the time of finalization of this review, no new trade name has been proposed for the product. The proposed indication is for diluting or dissolving drugs for intravenous,

intramuscular or subcutaneous injection.. The dosage forms of the product are 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL fill in 6 mL syringes and 2 mL, 5 mL and 10 mL fill in 12 mL syringes for single use.

These saline filled syringe products were developed under IND (b) (4). The Division of Gastrointestinal and Hematology Products (DGHP) and Medefil Inc. had scheduled a pre-IND/pre-NDA meeting on July 14, 2008, regarding a development program and registration requirements of these saline products (1, 2, 2.5, 3 and 5 mL saline in a (b) (4) ML syringe). Medefil submitted a meeting package on May 14, 2008. DGHP reviewed the package and sent responses to the Medefil's questions on July 11, 2008. Medefil was satisfied with the responses and the meeting was canceled. In the pre-meeting response, the Agency agreed with the Applicant regarding the clinical developmental program of the proposed product:

- No non-clinical studies are required;
- No clinical studies are required;
- The proposed product does not raise pharmacokinetic issues;

This product has also been evaluated by CDRH under the 510(k) process and it was determined to be "substantially equivalent to legally marketed predicate devices", and, thus, could be marketed as a device with the intention for use of flushing compatible intravenous tubing and/or indwelling intravenous access devices (The Letter from Anthony D. Watson, BS, MS, MBA, Director, Division of Anesthesiology, General Hospitals, Infection Control, and Dental Devices, CDRH, FDA, 02/03/2011).

Medefil submitted the NDA application to the Division of Gastroenterology Products on January 31, 2011 and it was received on February 1, 2011. However, the submission was incomplete and was not accepted for filing since the appropriate user fee was not received at the time of the submission. Subsequently, the user fee for this application was waived on March 7, 2011. Therefore, the application has been accepted as of March 7, 2011. The PDUFA action date is January 7, 2012. In addition, CDER reassigned the application to the Division of Pulmonary, Allergy, and Rheumatology Products on March 7, 2011.

2.1 Product Information

The proposed product is normal saline (0.9% sodium chloride) in pre-filled syringes. Two sizes (6 and 12 mL in capacity) of syringes are being proposed. The respective filling volume will be 1, 2, 2.5, 3 or 5 milliliters in a 6-mL syringe and 2, 5 or 10 milliliters in a 12-mL syringe.

2.2 Tables of Currently Available Treatments for Proposed Indication

There are many approved and currently marketed saline products on the market. The following few are examples:

NDA 19-217, Sodium Chloride 0.9% in Plastic Container, Injectable Injection. 9MG/ML

NDA 16-366, Sodium Chloride 0.9% in Plastic Container, Injectable Injection.
900MG/100 ML

NDA 16-677, Sodium Chloride 0.9% in Plastic Container, Injectable Injection. Multiple Strengths

NDA 17-427, Sodium Chloride 0.9% in Plastic Container, Solutions; Irrigation.
900MG/100ML

NDA 21-569, Sodium Chloride 0.9% in Plastic Container, Injectable Injection. Multiple Strengths

ANDA 76-316, Sodium Chloride 0.9% in Plastic Container, Injectable Injection.
900MG/100 ML

ANDA 77-407, Sodium Chloride 0.9% in Plastic Container, Injectable Injection. 9MG/ML

ANDA 88-912, Sodium Chloride 0.9% in Plastic Container, Injectable Injection. 9MG/ML

3 Ethics and Good Clinical Practices

Not applicable because no clinical data were submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Because the proposed product is a combination of saline and a syringe that is a CDRH approved device, an Intercenter Request for Consultative or Collaborative Review Form was sent to CDRH May 6, 2011. In a Memorandum dated August 5, 2011, the CDRH reviewer recommended that the Applicant conduct a human factors study to evaluate user-related risks and user-performance, because the proposed product is intended to be used by health care providers and by patients as well. In the mid-cycle review meeting on August 10, the review team, including the CDRH reviewer, discussed the recommendation. The consensus from the review team discussion is that a human

factors study will not be necessary for the proposed product used for the labeling indication: diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection. The rationale of this consensus is summarized as the following:

- The review team agreed that certain training would be necessary for a patient to correctly use the proposed product, 0.9% sodium chloride injection. However, the patient would have received needed training and obtained skills, if not more, to correctly use the proposed product, when the patient was directed to dilute/dissolve a drug and to inject it, or to irrigate/flush compatible intravenous tubing and / or indwelling access devices. Therefore, a human factors study for the proposed product would have no significant impact on user performance and user-related risk.
- There are many approved and currently marketed saline injection products on the market. No human factors study was required for those products.

5 Sources of Clinical Data

Not applicable because no clinical data were submitted.

6 Review of Efficacy

There are no clinical studies for efficacy submitted in this NDA.

6.1 Indication

The proposed drug indication for sodium chloride injection, USP, 0.9% syringes is for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered.

The same syringes are currently marketed as a medical device for irrigating and flushing compatible intravenous tubing and/or indwelling access devices.

7 Review of Safety

There are no safety studies submitted in this NDA. The Applicant is relying on the Agency's previous determination of safety for the reference 0.9% sodium chloride injection to support the proposed product.

7.7 Additional Submissions / Safety Issues

In the 74-day letter, the Applicant was asked to “Submit a summary and update of safety information of the proposed product per regulation 21 CFR 314.50(d)(5)(vi).” In the response received by the Agency on July 5, 2011, the Applicant states that “safety information and clinical evaluation of the 0.9% Normal Saline Injection is equivalent in terms of intended use as other normal saline IV flush syringe devices regularly placed on the market. A normal saline IV flush syringe is manufactured by Medefil, Inc. under current Good Manufacturing Practices and Quality System Regulations and conforms to the requirements of UP and EP Pharmacopoeias under the Sodium Chloride Injection monograph.”

The Applicant also attached the following 15 abstracts of published articles to support the safety of the proposed product. These abstracts reported the safe use of saline or heparinised saline in flush or irrigation to maintain patency of arterial and venous lines and devices.

1. Kannan, A., “Heparinised Saline or Normal Saline?”, *J. Perioper. Pract*, Vol. 18, No. 10, 2008, pp 440 – 1
2. Hadaway, L., “Technology of Flushing Vascular Access Devices”, *J. Infus. Nurs.*, Vol. 29, No. 3, 2006, pp 129 – 45
3. Whitta, R.K., Hall, K.F., Bennets, T.M., Welman, L., and Rawlins, P., “Comparison of Normal or Heparinised Saline flushing on function of Arterial Lines”, *Crit. Care. Resuc.*, Vol. 8, No. 3, 2006, pp. 205 – 8
4. Lapum, J.L., “Patency of Arterial Catheters with Heparinised Solutions versus Non – Heparinised Solutions: A Review of the Literature”, *Can. J. Cardiovasc. Nurs.*, Vol. 16, No. 2, 2006, pp. 64 – 70
5. Kulkarni, M., Elsner, C., Ouellet, D. and Zeldin, R., “Heparinised Saline versus Normal Saline in Maintaining Patency of the Radial Artery Catheter”, *Can. J. Surg.*, Vol. 27, No. 1, 1994, pp. 37 – 42
6. Zevola, D.R., Dioso, J. and Moggio, R., “Comparison of Heparinised and Non-heparinized Solutions for Maintaining Patency of Arterial and Pulmonary Artery Catheters”, *Am. J. Crit Care*, Vol. 6, No.1, 1997, pp. 52 – 5
7. Del Cotillo, M., Grane, M., Llavore, M. and Quintana, S., “Heparinised Solution versus Saline Solution in the Maintenance of Arterial Catheters: A Double Blind Randomized Clinical Trial”, *Intensive Care Med.*, Vol. 34, No.2, 2008, pp. 339 – 43

8. LeDuc., L., “Efficacy of Normal Saline Solution versus Heparin solution for Maintaining Patency of Peripheral Intravenous Catheters in Children”, *J. Emerg. Nurs.*, Vol. 23, No. 4, 1997; pp. 306 – 9
9. Kleiber, C., Hanrahan, K., Fagan, C.L. and Zittergruen, M.A., “Heparin versus Saline for Peripheral I. V. Locks in Children”, *Pediatr. Nurs.*, Vol. 19, No. 4, 1993, pp. 405 – 9
10. Niesen, K.M., Harris, D.Y., Parkin, L.S. and Henn, L.T., “The Effects of Heparin versus Normal Saline for Maintenance of Peripheral Intravenous Locks in Pregnant Women”, *J. Obstet. Gynecol. Neonatal Nurs.*, Vol. 32, No. 4, 2003, pp. 503 – 8
11. Meyer, B.A., Little, C.J., Thorp, J.A., Cohen, J.R. and Yeast, J.D., “Heparin versus Normal Saline as a Peripheral Line Flush in Maintenance of Intermittent Intravenous Lines in Obstetric Patients”, *Obstet. Gynecol.*, Vol. 85, No. 3, 1995, pp. 433 – 6
12. Mudge, B., Forcier D. and Slattery, M.J., “Patency of 24 – gauge Peripheral Intermittent Infusion Devices: A Comparison of Saline and Heparin Flush Solutions”, *Pediatr. Nurs.*, Vol. 24, No. 2, 1998, pp. 142 – 5
13. Clifton., G.D., Branson, P., Kelly, H.J., Dotson, L.R., Record, K.E., Phillips, B.A. and Thompson, J.R., “Comparison of Normal Saline and Heparin Solutions for Maintenance of Arterial Catheter Patency”, *Heart Lung*, vol. 20, No. 2, 1991, pp. 115 – 8
14. Mok, E., Kwong, T.K. and Chan, M.F., “A randomized controlled trial for maintaining peripheral intravenous lock in children”, *Int. J. Nurs. Pract.*, Vol. 13, No. 1, 2007, pp. 33 – 45
15. Robertson, J., “Intermittent intravenous therapy: a comparison of two flushing solutions”, *Contemp. Nurs.*, Vol. 3, No. 4, 1994, pp. 174 – 9

8 Postmarket Experience

No post-marketing data were submitted.

9 Appendices

9.2 Labeling Recommendations

The Applicant submitted the proposed product labeling in the appropriate PLR format. The labeling was reviewed by all the disciplines and by the Division of Drug Marketing Advertising and Communication (DDMAC). The revised label was communicated to the Applicant on November 23, 2011, and a response was received on December 6, 2011. At the time of this review, final label discussions are continuing. One specific labeling issue which was addressed is that the Applicant

(b) (4)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XU WANG
12/08/2011

ANTHONY G DURMOWICZ
12/08/2011
I concur with Dr. Wang's clinical review.

MEDICAL OFFICER REVIEW			
Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)			
APPLICATION:	NDA 202832	TRADE NAME:	(b) (4)
APPLICANT/SPONSOR:	Medefil, Inc.	USAN NAME:	Sodium Chloride Injection, USP, 0.09% in plastic syringes
MEDICAL OFFICER:	Xu Wang, M.D., Ph.D.	TEAM LEADER:	Anthony G. Durmowicz, M.D.
DATE:	3/30/2011	CATEGORY:	Saline (diluting or dissolving drugs)
		ROUTE:	Injection
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
1/31/2011	2/02/2011	NDA 202832	Paper submission
RELATED APPLICATIONS			
<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>	
07/11/2008	IND (b) (4)	Response to pre-NDA questions (Division of Gastroenterology Products)	
<p>REVIEW SUMMARY: This is a 505(b)(2) application for Sodium Chloride Injection, USP, 0.09% in plastic syringes submitted by Medefil, Inc. The proposed trade name for the product is (b) (4). The proposed indications are for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection and for irrigating and flushing compatible intravenous tubing and / or indwelling access devices. The dosage forms of the product are 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL fill in 6 mL syringe and 2 mL, 5 mL and 10 mL fill in 12 mL syringe for single use. As a basis for the 505(b)(2) submission route, the applicant cites Hospira's 0.09% Sodium Chloride Injection, USP, in fliptop plastic vial as the reference drug.</p> <p>The Applicant discussed their product development plan with the Division of Gastroenterology Products in July 2008. The Agency concurred that no clinical studies would be required for the proposed product Chloride Injection, USP, 0.09% in plastic syringes [IND (b) (4), Draft response for pre-NDA meeting, Cristil Stark, M.S., Division of Gastroenterology Products, 07/11/2008]. Based on the pre-NDA discussion with the Agency, the NDA submission is fileable. There are no clinical data to review, the clinical review will be a background summary of this NDA submission. The Center for Devices and Radiological Health (CDRH) determined previously that the syringe "is substantially equivalent to legally marketed predicate devices", and the Applicant "may market the device" [The Letter from Anthony D. Watson, BS, MS, MBA, Director, Division of Anesthesiology, General Hospitals, Infection Control, and Dental Devices, CDRH, FDA, 02/03/2011]. For this NDA submission, a CDRH inter-center consultation will be requested.</p> <p>The NDA is a paper submission including only CMC data. There are no clinical section (Module 5) including clinical overview and summary in this NDA submission. The Applicant will be asked to provide a summary and update of safety information of the proposed product per regulation 21 CFR 314.50 (d)(5)(vi). Proposed labeling has been included in this submission. The content of the proposed labeling is similar to that of the reference product. An OSE labeling review consultation will be requested.</p> <p>The NDA was submitted on January 31, 2011, and received on February 1, 2011. However, the submission was incomplete and was not accepted for filing since the appropriate user fee was not received at the time of the submission. The user fee for this application was waived on March 7, 2011. Therefore, the application has been accepted as of March 7, 2011. The PDUFA action date is January 7, 2012.</p> <p>There is one clinical comment to the Applicant.</p> <p>OUTSTANDING ISSUES: There are no clinical data in this submission.</p>			
RECOMMENDED REGULATORY ACTION			
NDA/SUPPLEMENTS:	FILABLE <input checked="" type="checkbox"/>	NOT FILABLE _____	
	APPROVAL _____	APPROVABLE _____	NOT APPROVABLE _____
OTHER ACTION:	COMMENTS FOR SPONSOR <input checked="" type="checkbox"/>		

NDA 202832 (b) (4) (Sodium Chloride Injection, USP, 0.9%)
Medefil, Inc. 01/31/2011

Reviewed by:

Xu Wang, M.D., Ph.D.
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Anthony G. Durmowicz, M.D.
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc: NDA 202832
HFD-570/Division File
HFD-570/ Durmowicz /Medical Team Leader
HFD-570/Wang/Medical Reviewer
HFD-570/Pei/Pharmacology-Toxicology Reviewer
HFD-570/Chung-Davis/CSO

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ YES ___

(While the NDA is fileable, there is no clinical section in the submission for a clinical review. The Applicant will be asked to provide a summary and update of safety information of the proposed product per regulation 21 CFR 314.50 (d)(5)(vi).)

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

NDA 202832, (b) (4) (Sodium Chloride Injection, USP, 0.9%)
Medefil, Inc. 01/31/2011

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Following clinical comment will be conveyed to the Applicant:

Submit a summary and update of safety information of the proposed product per regulation 21 CFR 314.50 (d)(5)(vi). The safety information should include available data from clinical studies, published literatures, and post-marketing adverse event reports.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XU WANG
04/15/2011

ANTHONY G DURMOWICZ
04/15/2011